IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOVAIL LABORATORIES INTERNATIONAL SRL a corporation of Barbados, Plaintiff, v. ANDRX PHARMACEUTICALS, LLC and ANDRX CORPORATION, Defendants.	C.A. No. 05-586 (KAJ)

DECLARATION OF MATTHEW C. MARLOWE IN SUPPORT OF ANDRX'S REPLY TO BIOVAIL'S OPPOSITION TO CONSOLIDATING BIOVAIL'S TWO SEPARATE ACTIONS ALLEGING INFRINGEMENT OF THE SAME PATENT AGAINST THE SAME ANDRX DEFENDANT

I, Matthew C. Marlowe, declare as follows:

1. I am an attorney and a member of the law firm Foley & Lardner LLP, counsel for Andrx Pharmaceuticals, LLC, and Andrx Corporation (collectively "Andrx").

2. My business address is 3000 K St. N.W., Suite 500, Washington, DC 20007.

3. I make this declaration in support of Andrx's Reply to Biovail's Opposition to Consolidating Biovail's Two Separate Actions Alleging Infringement of the Same Patent Against the Same Andrx Defendant.

4. Attached as Exhibit E is a true and correct copy of a facsimile from Matthew C. Marlowe to Preston K. Ratliff II, Esq., dated December 29, 2005. I have circled portions of this exhibit to indicate their special relevance.

5. Attached as Exhibit F is a true and correct copy of excerpts from Biovail's First Set of Requests for Documents and Things to Defendant Andrx, dated November 4, 2005. I have circled portions of this exhibit to indicate their special relevance.

6. Attached as Exhibit G is a true and correct copy of pages from Biovail's website at www.biovail.com, including the prescribing information accessible from that site on January 10, 2006 and January 13, 2006. I have circled portions of this exhibit to indicate their special relevance. Information of special relevance to (1) United States patients, and (2) United States health care professionals is marked with the numbers "1" and "2" respectively.

I swear under penalty of perjury that the foregoing is true and correct.

Matthew C. Marlowe

1/13/2006

Date

EXHIBIT E

FOLEY

FOLEY & LARDNER LLP
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WRITER'S DIRECT LINE
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CLIENT/MATTER NUMBER
054657-0103

December 29, 2005

Preston K. Ratliff II, Esq.
Fitzpatrick, Cella, Harper & Scinto
30 Rockefeller Plaza
New York, NY 10112-3801

Re: Biovail v. Andrx Pharmaceuticals LLC et al.,
Civil Action No. 1:05-cv-586

Dear Mr. Ratliff:

I am writing in response to your letter of December 28th.

First, it is unfortunate that you waited until December 28th – just 2 days before the target production date of December 30th – to identify documents that you wished Andrx to re-produce from its prior production. We will look into whether Andrx still has the Bates numbered documents on your list, and arrange for re-production as soon as reasonably possible.

Second, there is nothing more to confer about with respect to Biovail's position that it need not produce documents relating to invalidity on the ground that Andrx's invalidity allegations are somehow insufficient. Biovail had a chance to challenge the sufficiency and/or clarity of Andrx's allegations at the time Andrx filed them. Biovail chose not to do so. The allegations of validity are in the case, and Biovail will be subject to sanctions for refusing to provide the requested discovery, which Biovail concedes to be relevant to the issue of invalidity. This is just another instance of Biovail's litigation misconduct and violation of its duty to expedite this case. We will take this to Judge Jordan.

Third, Biovail's failure to return the allegedly "damaged" and "unusable" samples makes it difficult to conclude that you were being altogether truthful in asserting the "damage" as the reason for needing additional samples. We stand by our offer to replace the "damaged" samples once you return them to us. The rest of your complaints about samples are simply ridiculous. Andrx cannot provide samples of materials that it does not have. Just because you want something does not mean that it exists.

Fourth, we find equally fatuous your complaint about the term "on its face" in connection with determining whether a document is responsive. It means that we determine responsiveness

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by looking at the documents themselves that we pull from the files that are reasonably likely to contain at least some relevant documents.

Very Truly Yours,

Matthew C. Marlowe

cc: Jack Blumenfeld
William Cattie
Martin Endres

12/29/2005 16:49 FAX 001

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                    ******************************
                    ***   MULTI TX/RX REPORT   ***
                    ******************************

TX/RX NO                1448
PGS.                    3
TX/RX INCOMPLETE
                        -----
TRANSACTION OK
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                        (2)   9106#054657#0103#12123028998#
                        (3)   9016#054657#0103#13027781400#
                        (4)   9106#054657#0103#13024253012#
ERROR INFORMATION
                        -----
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FACSIMILE TRANSMISSION

Total # of Pages (including this page): 3

TO:	PHONE #:	FAX #:
Preston K. Ratliff II, Esq		(212) 218-2200
Martin Endres, Esq.		(212) 302 8998
William J. Cattie III, Esq.		(302) 778 1400
Jack Blumenfeld, Esq.		(302) 425-3012

From : Matthew C. Marlowe
Email Address : mmarlowe@foley.com
Sender's Direct Dial : 202.672.5391
Date : December 29, 2005
Client/Matter No : 054657 - 0103
User ID No :

MESSAGE: PLEASE SEE ATTACHED.

EXHIBIT F

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOVAIL LABORATORIES INTERNATIONAL SRL a corporation of Barbados, Plaintiff, v. ANDRX PHARMACEUTICALS, LLC and ANDRX CORPORATION, Defendants.	C.A. No. 05-586 (KAJ)

BIOVAIL'S FIRST SET OF REQUESTS FOR DOCUMENTS AND THINGS TO DEFENDANT ANDRX

Pursuant to Rule 34 of the Federal Rules of Civil Procedure and Local Civil Rules 5.4 and 26.1 of the United States District Court for the District of Delaware, Plaintiff Biovail Laboratories International SRL ("Biovail") requests that Defendants Andrx Pharmaceuticals, LLC and Andrx Corporation (collectively "Andrx") produce documents in response to the following requests, in accordance with the following Definitions and Instructions. Unless otherwise agreed, production is to be made at the offices of Fitzpatrick, Cella, Harper & Scinto, 30 Rockefeller Plaza, New York, NY 10112.

5. The term "the '791 patent" means United States Patent No. 5,529,791 entitled "Extended Release Form Of Diltiazem".

6. The term "diltiazem hydrochloride compositions" means any drug product(s) that includes diltiazem hydrochloride as its active ingredient, regardless of the name or designation used in a particular document or thing.

7. The term "defendant's diltiazem hydrochloride composition(s)" means the drug products, including but not limited to, the active ingredient and all other components (including excipients) which comprise each strength of each drug product which is the subject of ANDA No. 77-686, and any other diltiazem hydrochloride product which defendant has tested, evaluated, purchased, or otherwise acquired or sold.

8. The term "FDA" means the United States Food and Drug Administration.

9. The term "NDA" means New Drug Application.

10. The term "ANDA" means Abbreviated New Drug Application.

11. The term "plaintiff's NDA" means NDA No. 21-392.

12. The term "defendant's ANDA" means ANDA No. 77-686, including any updates, supplements, amendments, revisions, etc.

13. The term "prior art" encompasses, by way of example and without limitation, the subject matter described in each and every subdivision of 35 U.S.C. § 102 and 35 U.S.C. § 103.

14. The term "excipient" means, for the basis of these requests only, any substance other than the active ingredient in a drug composition.

15. The term "calcium channel blocker" or "CCB" means any composition that blocks the entry of calcium into a cell.

a. all associated file labels, file headings, and file folders shall be produced together with the responsive documents from each file, and each file shall be identified as to its owner or custodian;

b. all documents that cannot be legibly copied shall be produced in their original form; otherwise, defendants may produce photocopies; and

c. each page shall be given a discrete production number.

REQUESTS

Request No. 1

All documents and things relating to or concerning defendant's communications with the FDA relating to diltiazem hydrochloride compositions.

Request No. 2

All documents and things relating to or concerning any consideration given by defendant of filing an ANDA for diltiazem hydrochloride compositions.

Request No. 3

All documents and things relating to or concerning defendant's decision to file an ANDA for diltiazem hydrochloride compositions, including but not limited to, Board of Director meeting minutes, business plans, etc.

Request No. 4

All documents and things relating to or concerning defendant's decision to file an amendment for additional dosage strengths to defendant's ANDA, including but not limited to, Board of Director meeting minutes, business plans, etc.

Request No. 5

All documents and things relating to or concerning defendant's ANDA.

Request No. 6

All documents and things within defendant's ANDA.

Request No. 7

All documents and things relating to or concerning the Paragraph IV certification notice letters of June 22, 2005 and August 30, 2005, including but not limited to, any drafts of these letters or any discussions of the substance, content, wording or format of the letters.

Request No. 8

All documents and things relating to or concerning the timing, schedule, timetable or approval of defendant's ANDA.

Request No. 9

All documents and things relating to or concerning the timing, schedule, timetable or approval of defendant's letters of June 22, 2005 and August 30, 2005 to Biovail.

Request No. 10

All meeting minutes or notes describing discussions about diltiazem hydrochloride compositions.

Request No. 11

All meeting minutes or notes describing or reflecting discussions about defendant's ANDA and the decision to file such ANDA, including but not limited to, the decision to file an amendment for additional dosage strengths to its ANDA.

Request No. 18

All documents and things relating to or concerning any marketing survey or study relating to diltiazem hydrochloride compositions and/or any other CCB.

Request No. 19

All documents and things relating to or concerning defendant's diltiazem hydrochloride product(s).

Request No. 20

All documents and things relating to or concerning defendant's diltiazem hydrochloride product(s) that are the subject of defendant's ANDA No. 77-686.

Request No. 21

All documents and things, including but not limited to, notebooks, meeting minutes, analyses, development reports, excipient reports and any other reports, concerning research, development, or production relating to the formulation of any diltiazem hydrochloride composition, done by or for defendant.

Request No. 22

All documents and things, including but not limited to, notebooks, meeting minutes, analyses, development reports, excipient reports and any other reports, relating to or concerning the formula, chemical composition, and physical characteristics of defendant's proposed diltiazem hydrochloride product(s).

any CCB in the marketplace.

MORRIS, NICHOLS, ARSHT & TUNNELL

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November 4, 2005

EXHIBIT G

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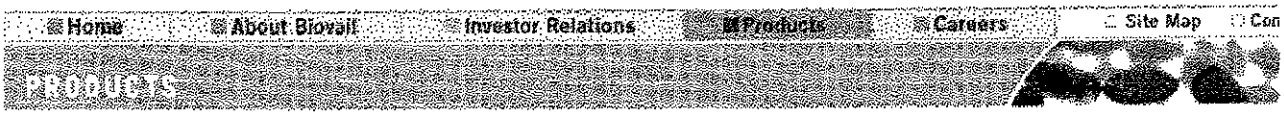
12/21/2005 1:56 PM
Biovail Submits Citizen Petition to FDA

12/21/2005 8:31 AM
Biovail Receives FDA Approval for Citalopram ODT

12/13/2005 4:09 PM
Depomed, Biovail Revise Partnership Agreement for Development, Commercialization of Glumetza(tm); Depomed to Have Rights for United States; Biovail to Have Rights for Canada

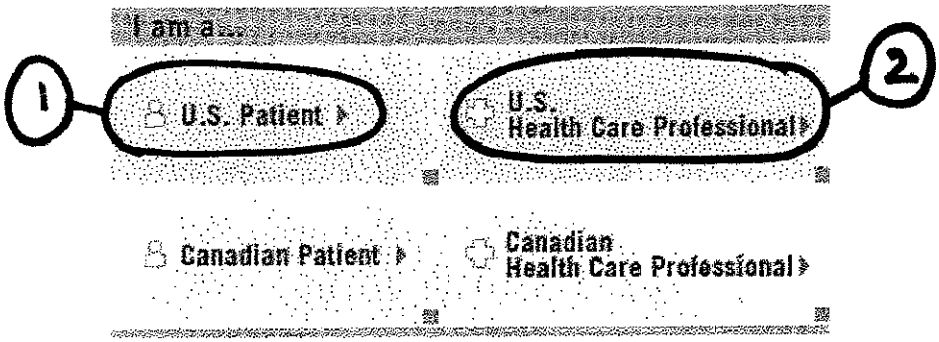
Steinbach Career Opportunities

2004 Interactive Annual Report



Information on Biovail products is available to patients and health care professionals. The Patient section features product profiles and other important information on Biovail's products. The Health Care Professional section includes complete prescribing information, reformulation data and other information of interest to physicians, pharmacists and other health care professionals.

To access the appropriate product information, select your country of residence, indicating if you are a patient or health care professional.



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(1)

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PRODUCTS

Our Products
- CARDIZEM® CD
- ZOVIRAX® Ointment
- VASOTEC®
- VASERETIC®
- CARDIZEM® LA
- ZOVIRAX® Cream
- ATIVAN®
- ISORDIL®

Biovail markets a range of quality pharmaceutical products in a number of therapeutic categories, including cardiology, diabetes, smoking cessation and depression. Products in Biovail's portfolio include controlled-release products developed by Biovail, as well as select products that have been licensed from other companies. Biovail is committed to expansion of its product lineup with the ongoing addition of quality products that meet the needs of patients. The following Biovail products are currently available in Canada. For patient information, click on the product of your choice.

ZOVIRAX® Ointment
Herpes Virus

CARDIZEM® LA
High Blood Pressure (Hypertension) / angina

ZOVIRAX® Cream
Herpes Virus (Cold Sores)

Additional Biovail Products

CARDIZEM® CD -	Chest Pain (Angina), High Blood Pressure (Hypertension)
VASOTEC® --	High Blood Pressure, Heart Failure
VASERETIC® --	High Blood Pressure
ATIVAN® --	Anxiety Disorders
ISORDIL® --	Angina

If you have medical information questions or need to report an adverse event or product complaint, please contact the Biovail Medical Communications Center at 1-866-BIOVAIL (246-8245), option 3 by phone, or (908) 927-1850 by fax, or Email Med.Comm@BIOVAIL.com

Privacy Policy Discla

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(1)

CARDIZEM® LA

USA

CARDIZEM® LA (diltiazem hydrochloride) brings new technology to well accepted antihypertensive control with diltiazem, a calcium channel blocker (CCB). CARDIZEM® LA features a new graded extended-release tablet formulation that provides 24-hour BP control. As a CCB, CARDIZEM® LA works by relaxing the coronary arteries and increasing the volume of blood that can circulate through them, thus reducing BP.

CARDIZEM® LA is generally well tolerated, with no significant increases in adverse events up to 540 mg QD. At the highest recommended daily dose (540 mg), the most commonly reported adverse events greater than placebo were lower-limb edema (8%), sinus congestion (2%), and rash (4%).

Please see full Prescribing Information .

CARDIZEM® LA is contraindicated in patients with sick sinus syndrome or 2° or 3° AV block (except in the presence of a functioning ventricular pacemaker), hypotension(<90mm Hg systolic), demonstrated hypersensitivity to the drug, and acute myocardial infarction and pulmonary congestion documented by x-ray on admission. Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (See WARNINGS).

Product information on this page is intended for residents of the U.S. only. Residents of Canada should return to the User Profile Selection page and select accordingly.

If you have medical information questions or need to report an adverse event or product complaint, please contact the Biovail Medical Communications Center at 1-866-BIOVAIL (246-8245), option 3 by phone, or (908) 927-1850 by fax, or Email Med.Comm@BIOVAIL.com

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2

PRODUCTS

Our Products
- CARDIZEM® CD
- ZOVIRAX® Ointment
- VASOTEC®
- VASERETIC®
- CARDIZEM® LA
- ZOVIRAX® Cream
- ATIVAN®
- ISORDIL®

Product Pipeline

Biovail markets a range of quality pharmaceutical products in a number of therapeutic categories, including cardiology, endocrinology, and central nervous system. Products in Biovail's portfolio include controlled-release products developed by Biovail, as well as select products that have been licensed from other companies. Biovail is committed to the expansion of its product lineup with the ongoing addition of quality products that meet the needs of health care professionals and their patients. The following Biovail products are currently available in Canada. For further information, click on the product of your choice.

ZOVIRAX® Ointment
Herpes Virus Prescribing Information

CARDIZEM® LA
High Blood Pressure (Hypertension) / angina Prescribing Information

ZOVIRAX® Cream
Herpes Virus (Cold Sores) Prescribing Information

Additional Biovail Products

CARDIZEM® CD -	Chest Pain (Angina), High Blood Pressure (Hypertension) Prescribing Information
VASOTEC® --	High Blood Pressure, Heart Failure Prescribing Information
VASERETIC® --	High Blood Pressure Prescribing Information
ATIVAN® --	Anxiety Disorders Prescribing Information
ISORDIL® --	Angina Prescribing Information

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(2)

CARDIZEM® LA

USA

CARDIZEM® LA (diltiazem hydrochloride) brings new technology to well accepted antihypertensive control with diltiazem, a calcium channel blocker (CCB). CARDIZEM® LA features a new graded extended-release tablet formulation that provides 24-hour BP control. As a CCB, CARDIZEM® LA works by relaxing the coronary arteries and increasing the volume of blood that can circulate through them, thus reducing BP.

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CARDIZEM® LA is contraindicated in patients with sick sinus syndrome or 2° or 3° AV block (except in the presence of a functioning ventricular pacemaker), hypotension(<90mm Hg systolic), demonstrated hypersensitivity to the drug, and acute myocardial infarction and pulmonary congestion documented by x-ray on admission. Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (See WARNINGS).

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(1) + (2)

Cardizem® LA
(Diltiazem Hydrochloride)

Extended Release Tablets

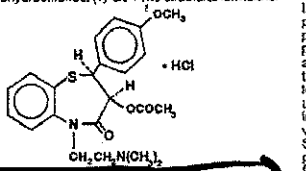
℞ only

Once-a-Day Dosage

PR0024-04 Rev. 04/04

DESCRIPTION

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-. The structural formula is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform. It has a molecular weight of 450.99. CARDIZEM® LA Tablets, for oral administration, are formulated as a once-a-day extended release tablet containing either 120 mg, 180 mg, 240 mg, 300 mg, 360 mg or 420 mg of diltiazem hydrochloride.

Also contains: Carnauba Wax NF, Colloidal Silicon Dioxide NF, Croscarmellose Sodium NF, Hydrogenated Vegetable Oil NF, Hypromellose USP, Magnesium Stearate NF, Microcrystalline Cellulose NF, Polyethylene Glycol NF, Pregelatinized Starch NF, Polyacrylate Dispersion 30%, Polyethylene Glycol NF, Polydextrose, Polysorbate NF, Povidone USP, Simethicone USP, Sodium Starch Glycolate NF, Sucrose Stearate, Talc USP, Titanium Dioxide USP.

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action

Hypertension. Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina. Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads. Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasms are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissues. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem causes relaxation of coronary smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and non-ischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Pharmacokinetics and Metabolism

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine. Drugs which induce or inhibit hepatic microsomal enzymes may alter diltiazem disposition.

Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites, which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem.

In vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem hydrochloride binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Minimum therapeutic plasma diltiazem concentrations appear to be in the range of 50 to 200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

CARDIZEM LA Tablets. A single 360 mg dose of CARDIZEM LA results in detectable plasma levels within 3 to 4 hours and peak plasma levels between 11 and 18 hours; absorption occurs throughout the dosing interval. The apparent elimination half-life for CARDIZEM LA Tablets after single or multiple dosing is 6 to 9 hours. When CARDIZEM LA Tablets were coadministered with a high fat content breakfast, diltiazem peak and systemic exposures were not affected indicating that the tablet can be administered without regard to food. As the dose of CARDIZEM LA Tablets is increased from 120 to 240 mg, area-under-the-curve increases 2.5-fold.

Pharmacodynamics and Clinical Studies

Like other calcium channel antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Such data has no predictive value with respect to effects in patients with poor ventricular function, and increased heart failure has been reported in patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem. Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate.

During dynamic exercise, increases in diastolic pressure are inhibited, while maximum achievable systolic pressure is usually reduced. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem reduces the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of diltiazem hydrochloride to patients in doses of up to 540 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (see WARNINGS).

Hypertension. In a randomized, double-blind, parallel-group, dose-response study involving 476 patients with essential hypertension, evening doses of CARDIZEM LA 120, 240, 360, and 540 mg were compared to placebo and to 360 mg administered in the morning. The mean reductions in diastolic blood pressure by ABPM at roughly 24 hours after the morning (4 AM - 8AM) or evening (8 PM -10 PM) administration (i.e., the time corresponding to expected trough serum concentrations) are shown in the table below:

Mean Change in Trough Diastolic Pressure by ABPM

Evening Dosing				Morning Dosing
120 mg	240 mg	360 mg	540 mg	360 mg
−2.0	−4.4	−4.4	−8.1	−6.4

A second randomized, double-blind, parallel-group, dose-response study (N=256) evaluated CARDIZEM LA following morning doses of placebo or 120, 180, 300, or 540 mg. Diastolic blood pressure measured by supine office cuff sphygmomanometer at trough (7 AM to 9 AM) decreased in an apparently linear manner over the dosage range studied. Group mean changes for placebo, 120 mg, 180 mg, 300 mg and 540 mg were −2.6, −1.9, −5.4, −6.1 and −8.6 mm Hg respectively. Whether the time of administration impacts the clinical benefits of antihypertensive treatment is not known.

Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects.

Angina. The effects of Cardizem LA on angina were evaluated in a randomized, double-blind, parallel-group, dose-response trial of 311 patients with chronic stable angina. Evening doses of 180, 360 and 420 mg were compared to placebo and to 360 mg administered in the morning. All doses of Cardizem LA administered at night increased exercise tolerance when compared with placebo after 21 hours. The mean effect, placebo-subtracted, was 20 to 28 seconds for all three doses, and no dose-response was demonstrated. Cardizem LA, 360 mg, given in the morning, also improved exercise tolerance when measured 25 hours later. As expected, the effect was smaller than the effects measured only 21 hours following nighttime administration. Cardizem LA had a larger effect to increase exercise tolerance at peak serum concentrations than at trough.

INDICATIONS AND USAGE

CARDIZEM LA is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications.

CARDIZEM LA is indicated for the management of chronic stable angina.

CONTRAINDICATIONS

Diltiazem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem (see ADVERSE REACTIONS section).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension.** Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some (see PRECAUTIONS).

PRECAUTIONS

General

Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem is both a substrate and an inhibitor of the cytochrome P-450 3A4 enzyme system. Other drugs that are specific substrates, inhibitors, or inducers of this enzyme system may have a significant impact on the efficacy and side effect profile of diltiazem. Patients taking other drugs that are substrates of CYP450, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping concomitantly administered diltiazem in order to maintain optimum therapeutic blood levels.

Beta-Blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combi-

(1) & (2)

nation therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis. Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Benzodiazepines. Studies showed that diltiazem increased the AUC of midazolam and triazolam by 3- to 4-fold and the C_{max} by 2-fold, compared to placebo. The elimination half-life of midazolam and triazolam also increase (1.5 to 2.5 fold) during coadministration with diltiazem. These pharmacokinetic effects seen during diltiazem coadministration can result in increased clinical effects (e.g., prolonged sedation) of both midazolam and triazolam.

Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.

The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Lovastatin. In a ten-subject study, coadministration of diltiazem (120 mg bid diltiazem SR) with lovastatin resulted in a 3 - 4 times increase in mean lovastatin AUC and C_{max} versus lovastatin alone; no change in pravastatin AUC and C_{max} was observed during diltiazem coadministration. Diltiazem plasma levels were not significantly affected by lovastatin or pravastatin.

Rifampin. Coadministration of rifampin with diltiazem lowered the diltiazem plasma concentrations to undetectable levels. Coadministration of diltiazem with rifampin or any known CYP 3A4 inducer should be avoided when possible, and alternative therapy considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 *mg/kg*/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights, pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use. Clinical studies of diltiazem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

In the hypertension study, the following table presents adverse reactions more common on diltiazem than on placebo (but excluding events with no plausible relationship to treatment), as reported in placebo-controlled hypertension trials in patients receiving a diltiazem hydrochloride extended-release formulation (once-a-day dosing) up to 540 mg.

	Placebo	Diltiazem hydrochloride extended-release	
Adverse Reactions (MedDRA Term)	n = 120 # pts (%)	120 - 360 mg n = 501 # pts (%)	540 mg n = 123 # pts (%)
Oedema lower limb	4 (3)	24 (5)	10 (8)
Sinus congestion	0 (0)	2 (1)	2 (2)
Rash NOS	0 (0)	3 (1)	2 (2)

In the angina study, the adverse event profile of CARDIZEM LA was consistent with what has been previously described for CARDIZEM LA and other formulations of diltiazem HCl. The most frequent adverse effects experienced by CARDIZEM LA-treated patients were edema lower-limb (6.8%), dizziness (6.4%), fatigue (4.8%), bradycardia (3.6%), first-degree atrioventricular block (3.2%), and cough (2%).

In clinical trials of other diltiazem formulations involving over 3200 patients, the most common events (i.e. greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%) and rash (1.2%).

In addition, the following events have been reported infrequently (less than 2%) in hypertension trials with other diltiazem products:

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), nausea, thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus.

Other: Albuminuria, allergic reaction, amblyopia, asthenia, CPK increase, crystalluria, dyspnea, ecchymosis, edema, epistaxis, eye irritation, headache, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, neck rigidity, nocturia, osteoarticular pain, pain, polyuria, rhinitis, sexual difficulties, gynecomastia.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and diltiazem therapy is yet to be established.

OVERDOSAGE

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases.

There have been 29 reports of diltiazem overdose in doses ranging from less than 1 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions.

Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure, and in cases of cardiac failure, inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences, the following measures may be considered:

Bradycardia: Administer atropine (0.60 to 1 mg). If there is no response to vagal blockage, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g., dopamine or norepinephrine). Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION

CARDIZEM LA Tablets are an extended release formulation intended for once-a-day administration.

Patients controlled on diltiazem alone or in combination with other medications may be switched to CARDIZEM LA Tablets once-a-day at the nearest equivalent total daily dose. Higher doses of CARDIZEM LA Tablets once-a-day dosage may be needed in some patients. Patients should be closely monitored. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited general clinical experience with doses above 360 mg, but the safety and efficacy of doses as high as 540 mg have been studied in clinical trials. The incidence of side effects increases as the dose increases with first-degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose.

The tablet should be swallowed whole and not chewed or crushed.

Hypertension

Dosage needs to be adjusted by titration to individual patient needs. When used as monotherapy, reasonable starting doses are 180 to 240 mg once daily, although some patients may respond to lower doses. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. The dosage range studied in clinical trials was 120 to 540 mg once daily. The dosage may be titrated to a maximum of 540 mg daily.

CARDIZEM LA Tablets should be taken about the same time once each day either in the morning or at bedtime. The time of dosing should be considered when making dose adjustments based on trough effects.

Angina

Dosage for the treatment of angina should be individualized based on response. The initial dose of 180 mg once daily may be increased at intervals of 7 - 14 days if adequate response is not obtained. CARDIZEM LA doses above 360 mg appear to confer no additional benefit.

CARDIZEM LA can be given once daily, either in the evening or in the morning.

Concomitant Use with Other Cardiovascular Agents

1. **Sublingual NTG.** May be taken as required to abort acute anginal attacks during Diltiazem Hydrochloride Extended-release therapy.
2. **Prophylactic Nitrate Therapy.** Diltiazem Hydrochloride Extended Release Tablets may be safely coadministered with short-and long-acting nitrates.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)
4. **Antihypertensives.** CARDIZEM LA has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of Diltiazem Hydrochloride Extended Release Tablets or the concomitant antihypertensives may need to be adjusted when adding one to the other.

HOW SUPPLIED

CARDIZEM LA is supplied as white, capsule-shaped tablets debossed with "B" on one side and the diltiazem content (mg) on the other.

	NDC # 64455-xxx-yy			
Strength	Qty 7	Qty 30	Qty 90	Qty 1000
120 mg	100-07	100-30	100-90	100-10
180 mg	101-07	101-30	101-90	101-10
240 mg	102-07	102-30	102-90	102-10
300 mg	103-07	103-30	103-90	103-10
360 mg	104-07	104-30	104-90	104-10
420 mg	105-07	105-30	105-90	105-10

Storage conditions: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature).
Avoid excessive [illegible] times above 30°C (86°F).

Dispense in tight, light resistant container as defined in USP.
Rx Only.

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